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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/492,954	Applicant(s) PYLE ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 6-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 6-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed March 25, 2004. Currently, claims 1-2, 6-8 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn in view of the amendments to the claims.

a. The rejection of Claim 6 over Eggleston or Kowalczykowski in view of Bjornson et al in view of Nazarenko has been withdrawn in view of the applicant's arguments with respect to the combinability of the references.

b. The 101 statutory double patenting rejection is no longer appropriate in view of the amendments to the claims. A provisional obvious type double patenting rejection may be found below in response to the amendments to the claims.

4. This action contains new grounds of rejection necessitated by amendment.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Response

It is noted that an IDS was filed on January 27, 2000. The IDS was considered on June 22, 2000 and mailed to applicant. There are numerous references on pages 41-44 of the specification which are not listed on this 1449. Thus, as stated previously, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

New Grounds of Rejection Necessitated by Amendment

New Matter

6. Claims 1-2, 6-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, references to "the nanomolar range" and "initially present at a concentration of 1-3 nanomolar" are included. The amendment proposes that the new claim language is supported by the specification, for example page 33, lines 13 and page 38, lines 24-30. However, the specification does not describe or discuss "the nanomolar range" and "initially present at a concentration of 1-3 nanomolar."

Instead the specification describes an unwinding reaction which states, "in a typical reaction, 1-2nM RNA substrate was incubated with 10-15nM NPH-II in reaction buffer..." (page 33, line 13). The specification further states that helicase reactions, "typical reaction, 3nM RNA substrate..."(page 38, lines 25-30). This description does

not support “the nanomolar range” or “initially present at a concentration of 1-3 nM”. The specification makes no mention of “initially present.” The nanomolar range encompasses partial and extremely large numbers of nM. The specification fails to contemplate “the nanomolar range.” The disclosure of two single examples over 1-3 nM does not support the genus or range of “the nanomolar range” of Claim 1.

The concept of “the nanomolar range” and “initially present at a concentration of 1-3 nanomolar” does not appear to be part of the originally filed invention. Therefore, to “the nanomolar range” and “initially present at a concentration of 1-3 nanomolar” constitutes new matter.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-2, 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-2, 6-8 are indefinite over the recitation “the nanomolar range” because it is unclear what “the nanomolar range” encompasses. The specification nor the claims sets forth the nanomolar range. Further, it is unclear what amount of RNA would be encompassed by the nanomolar range. It is unclear whether the nanomolar range encompasses fractions of a nanomole and whether there is some limit to the number of nanomoles. It is unclear whether the claim has any definite range which

constitutes "the nanomolar range." The claims have been broadly interpreted below for the purpose of art rejections.

B) Claim 2 is indefinite over the recitation "initially present at a concentration of 1-3 nanomolar." It is unclear what is meant by initially present. Claim 1, from which the claim depends fails to describe an initial step and a subsequent step. Further, there is no amplification or degradation step. Therefore, it appears that initially must mean some change occurs. It is unclear whether initially means that 1-3 nM are present and then more is present, such that some larger amount of RNA is present in the method. The metes and bounds of the claimed invention are unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-2 and 7-8 are rejected under 35 U.S.C. 103 (a) over Shuman (Proc. Natl. Acad. Sci. USA, November 1992, Vol. 89, pages 10935-10939) in view of Bjornson et al. (Biochemistry, (1994). Vol. 33, pages 14306-14316) as evidenced by Stern et al. (US Pat. 5,712,096, January 1998) and Karn et al. (US Pat. 6,316,194, Nov, 2001).

Shuman teaches a method for detecting the release of a single-stranded RNA from an RNA duplex which comprise admixing an RNA helicase with the RNA duplex under conditions permitting the RNA duplex to unwind the RNA duplex and release single stranded RNA, wherein the RNA duplex comprises a first RNA having a label and a second RNA wherein the unwound single-stranded RNA released from the duplex is detected by gel electrophoresis (Page 10936, Col. 1, lines 18-29, and 40-52. and Figures 1-2). Shuman teaches a method, wherein ATP and a divalent cation is present (Methods Section. Enzyme Assays Subsection). The enzyme assays used helicase reaction mixtures which contained Tris-HCL, 2mM dithiothreitol, mgCl2, GTP, 20-50 fmol of P-labeled standard dsRNA substrate (20,000,000-50,000,000 nM). Shuman teaches a method of measuring the rate of release of a single-stranded RNA from an RNA duplex which complies detecting whether the single-stranded RNA is released from the RNA duplex at predetermined time intervals, and detecting therefrom the rate of release of the single-stranded RNA from the RNA duplex (Results Section, Kinetics Subsection and Figure 2). Shuman teaches a method of determining whether a

compound is capable of modulating the release of a single-stranded RNA from an RNA duplex (Results Section, Requirements of Helicase Activity Subsection).

Shuman does not teach the method. wherein the first label is capable of producing a luminescent energy pattern wherein the first RNA is present in the RNA duplex which differs from the luminescent energy pattern produced when the first RNA is not present in the RNA duplex, thereby detecting release of a single-stranded RNA from the RNA duplex.

Shuman does not teach the method. wherein the first label is present at the 5' end of the first RNA and the second label is attached to the 3' end of the second RNA and the luminescent energy pattern results from interaction of luminescent energy released from the first label with the second label.

However Bjornson et al. teach the method, wherein the first label is capable of producing a luminescent energy pattern wherein the first nucleotide is present in the nucleic acid duplex which differs from the luminescent energy pattern produced when the first nucleotide is not present in the nucleotide duplex, thereby detecting release of a single-stranded nucleic acid from the nucleic acid duplex after admixing helicase (Abstract. and Results section). Bjornson teaches that the fluorescence assay is extremely sensitive allowing DNA unwinding reactions to be monitored continuously at DNA concentrations as low as **1nM** in a fluorescence stopped-flow experiment (abstract). Moreover, Bjornson et al.teach several advantages of using a fluorescent based assay for kinetic studies in general and particularly for mechanistic studies for helicase-catalyzed unwinding. Bjornson et al. teach the method, wherein the first label

is present at the 5' end of the first nucleic acid and the second label is attached to the 3' end of the second nucleic acid and the luminescent energy pattern results from interaction of luminescent energy released from the first label with the second label. Materials and Methods Section, Preparation of DNA unwinding subsection, and Results section and Figure 1).

Further, Stern teaches labeling both the 5' and 3' end of RNA. Stern teaches the RNA termini with fluorescein phosphoroamidites (3' labeling) or CPG (5' lablelin) or the incorporation of fluorescent adenosine or cytosine nucleotides at specific positions internal in the RNA (col. 15, lines 15-20).

Moreover, Karn teaches FRET labeleling of RNA. Karn teaches that the target RNA may be fluorescently labeled at the 3' or 5' end of a strand within the target RNA or within the chain of the target RNA. Karn teaches an entire section of fluorescent labeling which includes labeling with 2 fluorescent groups with one group laced adjacent to the 5' end of the target RNA and a second fluorescent group placed adjacent to the 3' end of the target (col. 11-12).

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have substituted and combined the method of Shuman in view of Bjornson. The ordinary artisan would have been motivated to have substituted the fluorescent labeling method of Bjornson for the radiolabeled method of Shuman. The ordinary artisan would have been motivated to have the first label that is capable of producing a luminescent energy pattern wherein the first nucleotide is present in the nucleic acid duplex which differs from the luminescent energy pattern

produced when the first nucleotide is not present in the nucleotide duplex. thereby detecting release of a single-stranded nucleic acid from the duplex after admixing helicase of Bjornson et al in the method of Schuman. The art clearly teaches that ability to label both the 5' and 3' end of RNA as well as DNA. Bjornson specifically states, "we describe a fluorescence assay that can be used to monitor helicase-catalyzed unwinding of duplex DNA continuously in real time (Abstract, first sentence). The ordinary artisan would have been motivated to have used a continuously real time assay in lieu of a radiolabeled method without the functionality of real time detection. Further motivation is provided by Bjornson, "this emphasizes the utility of the continuous spectroscopic method described here, which allows many more time points to be collected, thus enabling more accurate determinations of the complete time course and observed rate constants for all phase of a multiphasic reaction (Page 1431 6, Column 1, last sentence of the second paragraph). An ordinary artisan would have been motivated to have substituted and combined the method, wherein the first label is capable of producing a luminescent energy pattern wherein the first nucleotide is present in the nucleic acid duplex which differs from the luminescent energy pattern produced when the first nucleotide is not present in the nucleotide duplex, thereby detecting release of a single-stranded nucleic acid from the duplex after admixing helicase of Bjomson in the method of Schuman, in order to achieve the express advantages, as noted by Bjornson, of a fluorescence assay that can be used to monitor helicase-catalyzed unwinding of duplex nucleic acids continuously in real time and which emphasizes the utility of the continuous spectroscopic method described here

allowing many more time points to be collected, thus enabling more accurate determinations of the complete time course and observed rate constants for all phase of a multiphasic reaction.

Response to Arguments

The response traverses the rejection. The response asserts that "none of the cited references teach the detection of nanomolar amounts of fluorescently labeled RNA, nor do any of the cited references teach a duplex RNA having a different label at the 5' and 3' end of each antiparallel strand in the duplex." In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The response addresses each of the references presented in the rejection above (page 6 of response filed June 7, 2004) stating the deficiencies of each of the references. The response fails to address the motivation for substituting a fluorescence assay that can be used to monitor helicase-catalyzed unwinding of duplex DNA continuously in real time for a radioactive assay. It is noted that not one of the references individually teaches detection of nanomolar amounts of fluorescently labeled RNA, nor do any of the cited references teach a duplex RNA having a different label at the 5' and 3' end of each antiparallel strand in the duplex, however, the response does not appear to address the combination of the references as a whole. Shuman specifically teaches an RNA helicase method for analyzing release of ssRNA from RNA duplex. Bjornson teaches detecting DNA

helicase activity using 1nM and fluorescently labeled duplex DNA. The art teaches that RNA may be fluorescently labeled on both the 5' and 3' end. Thus, performing the RNA method of Shuman by substituting the fluorescent method of Bjornson in view of the state of the art would provide a method for detecting the release of ssRNA from RNA duplex using fluorescence. As provided above, the ordinary artisan would have been motivated to have used a continuously real time assay in lieu of a radiolabeled method without the functionality of real time detection. Further motivation is provided by Bjornson, "this emphasizes the utility of the continuous spectroscopic method described here, which allows many more time points to be collected, thus enabling more accurate determinations of the complete time course and observed rate constants for all phase of a multiphasic reaction (Page 1431 6, Column 1, last sentence of the second paragraph).

With respect to the newly added limitation of nanomoloar amounts and "the nanomolar range". The method of Shuman detects 20-50fmol which is 20,000,000-50,000,000 nM which is broadly encompassed by "the nanomolar range" since the specification and the claims do not appear to define what the nanomolar range encompasses. Bjornson teaches the fluorescence assay is extremely sensitive allowing DNA unwinding reactions to be monitored continuously at DNA concentrations as low as 1nM which is well within any defined nanomolar range. Therefore, the art suggest that the fluorescent assay for detecting unwinding may be monitored using a concentration of nucleic acid as low as 1nM.

Thus for the reasons above and those already of record, the rejection is maintained.

10. Claim 6 is rejected under 35 U.S.C. 103 (a) over Shuman (Proc. Natl. Acad. Sci. USA, November 1992, Vol. 89, pages 10935-10939) in view of Bjornson et al. (Biochemistry, (1994), Vol. 33, pages 14306-14316) further in view of Nazarenko et al. (US Pat. 5,866,336, February 1999).

Neither Shuman nor Bjornson teach the labels fluorescein isothiocyanate and rhodamine isothiocyanate.

However, Nazarenko et al. (herein referred to as Nazarenko) teaches an extensive list of suitable moieties that can be selected as donor or acceptors in FRET pairs (col. 17-18).

It would have been prima facie obvious to a practitioner having ordinary skill in the art at the time the invention was made to have substituted and combined the labels fluorescein isothiocyanate and rhodamine isothiocyanate of Nazarenko in the method of Schuman in view of Bjornson. Bjornson teaches using fluorescein and hexachlorofuorescein which are among the listed donors and acceptors. Therefore, using alternative donors and/or acceptors which were known in the art would have the ability to quench signals as the labels taught by Bjornson. Therefore, using equivalent labels in the method would have been obvious to the ordinary artisan. An ordinary artisan would have been motivated to substitute and combine the labels fluorescein isothiocyanatc and rhodamine isothiocyanate of Nazarenko in the method of Schuman in view or Bjornson because Nazarenko teaches that the FRET donors and acceptors are functional equivalents.

Response to Arguments

The response traverses the rejection. The response asserts Nazarenko does nothing to overcome the deficiencies of Shuman or Bjornson in failing to teach the detection of nanomolar amounts of fluorescently labeled RNA. This argument has been reviewed but is not convincing because the combination of teachings of Shuman or Bjornson render obvious the detection of nanomolar amounts of fluorescently labeled RNA for the reasons set forth above. Thus for the reasons above and those already of record, the rejection is maintained.

11. Claims 1-2, 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eggleston (Nucleic Acids Research, Vol. 24, No. 7, pages 1179-1186, 1996).

Eggleston et al. (herein referred to as Eggleston) teaches a helicase assay based upon the displacement of fluorescent nucleic acid binding ligands. The helicase assay is continuous, kinetic assay based on the displacement of the fluorescent dyes from dsDNA upon DNA unwinding. Eggleston analyzes several dyes including ethidium bromide to function as suitable reporter molecules. Eggleston teaches that a variety of fluorophores were examined to determine their utility as reporter molecules in a continuous helicase assay. Reactions using several of these dyes share the properties of having relatively low fluorescence in the presence of ssDNA and significant fluorescence enhancement upon binding to dsDNA (page 1180, col. 2). Eggleston teaches that they anticipate that this dye displacement assay can find widespread use in the study of RNA helicases, thereby suggesting a reasonable expectation of success.

Eggleston suggests that the dye displacement assay can be readily adapted for use with other DNA helicases, with RNA helicases and with other enzymes that act on nucleic acids.

Eggleston teaches the details of the fluorometric helicase assay and how the assay was performed, measured and optimized depending upon the dye and enzyme concentration used (page 1181, col. 1). For the fluorometric helicase assay, the DNA substrate was 10 uM (0.01 nM) nucleotides BamHI-digested pBR322 which is within "the nanomolar range." (page 1181, col. 1). The unwinding was initiated by the addition of ATP in excess of Mg2+ ion concentrations (limitations of Claim 8). As seen in the Figure 1, the nucleic acid is labeled at the 5' end. It is noted that the 5' end is not the 5' terminus. The 5' end is interpreted to mean nucleotides 5' of the middle of the nucleic acid (limitations of Claim 1). The assay is performed over a relative time, for example at 10 time intervals, see Figure 1 (limitations of Claim 7).

Eggleston teaches that H33258 displays the greatest dsDNA specificity relative to ssDNA followed by TO, EB and DAPI. Due to their specificity for dsDNA , strong fluorescence signal, and minimal fluorescence in the absence of DNA, the fluorophores DAPI, H33258 and TO were selected for further study.

Eggleston states that "the studies have focused on DNA helicases, but the dye displacement assay may provide a new means by which the unwinding activity of RNA helicases can be examined" (page 1185, col. 2). Eggleston teaches that "since this dye binds to RNA in addition to DNA, it is readily conceivable that RNA helicases may be amenable to this assay if an appropriate ligand, such as EB or perhaps, propidium

iodide, is utilized" (page 1185, col. 2). Eggleston teaches that "once this parameter is optimized for a particular substrate and enzyme, the dye-displacement assay gives results which are consistent with those obtained from other types of assays" (page 1185). Therefore, while Eggleston's studies focus primarily on DNA helicases, Eggleston specifically teaches that the method would be applicable to RNA helicases and there would be a reasonable expectation of success for the RNA helicases method. Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have performed the dye-displacement assay using RNA helicase to analyze and study the continuous unwinding of RNA using the method taught by Eggleston.

Response to Arguments

The response traverses the rejection. The response asserts Eggleston fails to teach end-labeled DNA or RNA (page 8 of response filed June 7, 2004). This argument has been reviewed but is not convincing because the claim id directed to a fluorescent label attached at its 5' end or at its 3' end (see Claim 1a). As specifically provided in the rejection above, ."it is noted that the 5' end is not the 5' terminus. The 5' end is interpreted to mean nucleotides 5' of the middle of the nucleic acid (limitations of Claim 1)." The response does not appear to address this broad interpretation of the claims in any detail.

The response further states that "the instant claims do not provide DNA methods or dye displacement assays of the type taught by Eggleston." This argument has been

thoroughly reviewed, but is not found persuasive because Eggleston teaches each limitation of the instant claims and does not appear to be distinguished by the response.

With respect to the newly added limitation of nanomoloar amounts and "the nanomolar range". The method detects 10 uM (0.01nM) which is broadly encompassed by "the nanomolar range" since the specification and the claims do not appear to define what the nanomolar range encompasses.

Thus for the reasons above and those already of record, the rejection is maintained.

12. Claims 1-2, 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kowalczykowski et al. (US Pat. 5,747,247, May 1998).

Kowalczykowski et al. (herein referred to as Kowalczykowski) teaches a helicase assay based upon the displacement of fluorescent nucleic acid binding ligands. The helicase assay is continuous, kinetic assay based on the displacement of the fluorescent dyes from dsDNA upon DNA unwinding. Kowalczykowski analyzes several dyes including ethidium bromide to function as suitable reporter molecules. Kowalczykowski teaches that a variety of fluorophores were examined to determine their utility as reporter molecules in a continuous helicase assay. Reactions using several of these dyes share the properties of having relatively low fluorescence in the presence of ssDNA and significant fluorescence enhancement upon binding to dsDNA (col 3, lines 30-45). Kowalczykowski teaches that they anticipate that this dye displacement assay can find widespread use in the study of RNA helicases, thereby

suggesting a reasonable expectation of success. Kowalczykowski suggests that the dye displacement assay can be readily adapted for use with other DNA helicases, with RNA helicases and with other enzymes that act on nucleic acids.

Kowalczykowski teaches the details of the fluorometric helicase assay and how the assay was performed, measured and optimized depending upon the dye and enzyme concentration used (col 7-8). For the fluorometric helicase assay, the DNA substrate was 10 uM (0.01nM) nucleotides BamHI-digested pBR322 which is within "the nanomolar range." The unwinding was initiated by the addition of ATP in excess of Mg2+ ion concentrations (limitations of Claim 2, 8). As seen in the Figure 1, the nucleic acid is labeled at the 5' end. It is noted that the 5' end is not the 5' terminus. The 5' end is interpreted to mean nucleotides 5' of the middle of the nucleic acid (limitations of Claim 3). The assay is performed over a relative time, for example at 10 time intervals, see Figure 1 (limitations of Claim 7).

Kowalczykowski teaches that H33258 displays the greatest dsDNA specificity relative to ssDNA followed by TO, EB and DAPI. Due to their specificity for dsDNA , strong fluorescence signal, and minimal fluorescence in the absence of DNA, the fluorophores DAPI, H33258 and TO were selected for further study.

Kowalczykowski states that "the dye displacement assay also provides a new means by which the unwinding activity of RNA helicases can be examined (col. 15, lines 4-5). Kowalczykowski teaches that "since this dye binds to RNA in addition to DNA, RNA helicases are likewise amenable to this assay if an appropriate ligand, such as EB or perhaps, propidium iodide, is utilized" (col. 15, lines 13-15). Kowalczykowski teaches

that "the dye displacement assay can be adapted for use with any helicase, whether it utilizes a DNA or RNA substrate, provided that a suitable, minimally-inhibitory nucleic acid binding dye is selected" (col. 15, lines 15-20). Therefore, while Kowalczykowski's studies focus primarily on DNA helicases, Kowalczykowski specifically teaches that the method would be applicable to RNA helicases and there would be a reasonable expectation of success for the RNA helicases method.

Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have performed the dye-displacement assay using RNA helicase to analyze and study the continuous unwinding of RNA using the method taught by Kowalczykowski.

Response to Arguments

The response traverses the rejection. The response asserts Kowalczykowski fails to render obvious the claimed invention for the same reasons as Eggleston. The rejection of Eggleston is addressed above and maintained. Thus for the reasons above and those already of record, the rejection is maintained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 1-2, 6-8 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of copending Application No. 10/182,362 in view of Bjornson et al.

This is a provisional obviousness-type double patenting rejection.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by or would have been obvious over, the reference claim(s). See e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Here, Claim 1-8 of copending Application No. 10/182,362 recites a method of detecting the release of single stranded RNA from RNA duplex with fluorescence assay. The method of copending Application No. 10/182,362 differs from the claims herein in that it fails to disclose detecting RNA duplex within "the nanomolar range." However, Bjornson teaches a helicase DNA unwinding assay which measures by fluorescence energy transfer which uses concentrations of nucleic acid as low as 1 nM. While the claims differ in RNA and DNA, there would be a reasonable expectation of success based upon the state of the art and the ability to label both RNA and DNA on both the 3'

and 5' ends that RNA concentrations as low as 1 nM would similarly have a reasonable expectation of success. Therefore, it would have been obvious to modify the method of Claims 1-8 of copending Application No. 10/182,362 such that the method would use RNA duplex in an amount within the nanomolar range.

Response to Arguments

The response previously indicated that applicant will consider canceling Claims 1-8 of copending Application No. 10/182,362 when the instant claims are otherwise deemed allowable. It is noted that the instant rejection has been amended in view of the amendments to the claims, such that the claims are no longer identical with copending Application No. 10/182,362. Therefore, a terminal disclaimer may be an appropriate means for overcoming the instant provisional rejection.

Conclusion

14. No claims allowable over the art.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg
Jeanine Goldberg
Patent Examiner
July 19, 2004